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EXAMINER	
FALK, ANNE MARIE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/917,126	ISACSON ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 16-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4 and 16-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 January 2002 and 04 August 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed September 19, 2005 (hereinafter referred to as "the response") has been entered. Claims 1, 16, 21, 25-27, 29, and 30 have been amended.

Accordingly, Claims 1, 4, and 16-32 remain pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on September 19, 2005 has been entered.

The rejection of Claims 16-18 and 30-32 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, due to the presence of new matter in the claims, is withdrawn in view of the amendments to the claims to now recite "100 to 50,000 cells per microliter."

The rejections under 35 U.S.C. 112, second paragraph, for indefiniteness, are withdrawn in view of the amendments to the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1, 4, and 16-32 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced in the Office Actions of 10/6/03 and 11/2/04, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

At page 6, paragraphs 3-4 of the response, Applicants assert that the claims have been amended to recite that a therapeutic effect is achieved by the method. Therefore, this aspect of the enablement rejection, relating to the fact that "no particular treatment effect is achieved," is withdrawn in view of the amendments to the claims.

At page 7, paragraphs 2-3 of the response, Applicants assert that the claims have been amended to remove reference to "serotonergic" neurons. Therefore, this aspect of the enablement rejection, relating to the lack of teaching in both the prior art and the instant specification that serotonergic neurons are useful in treating Parkinson's disease, is withdrawn in view of the amendments to the claims.

At page 7, paragraph 6 of the response, Applicants assert that the specification teaches a variety of methods for achieving transfection of embryonic stem cells. Applicants point to the specification at page 10, lines 6-12 for teaching that a recombinant molecule may be introduced into the embryonic stem cells or the cells differentiated from the stem cells using *in vitro* delivery vehicles or *in vivo* techniques. The specification states that examples of delivery techniques include retroviral vectors, adenoviral vectors, DNA virus vectors, liposomes, physical techniques such as microinjection, and transfection such as via electroporation, calcium phosphate precipitation, or other methods known in the art. Applicants further note that mouse ES cells were transfected with a vector encoding Nurr-1 using Lipofectamine as set forth in Examples 2, 9, and 10 of the specification. However, the guidance provided at page 10 of the specificaion is in the form of general guidance rather than specific guidance. The guidance is directed to

ES cells in general, including mouse ES cells as well as any other species of ES cell that may be used in developing the methods of the invention. However, the rejection is not based on the unpredictability for transfecting ES cells in general or mouse cells in particular, but rather **human** ES cells specifically. Where Applicants' arguments address the genetic modification of ES cells in general, rather than human ES cells specifically, the arguments are off-point; the rejection is not directed to ES cells in general or to mouse ES cells. Thus, the use of Lipofectamine transfection for mouse ES cells is not instructive with regard to human ES cells, as the instant specification does not teach that human ES cells should be transfected using Lipofectamine and the art shows that Lipofectamine transfection does not work for human ES cells (see Eiges et al., Figure 1). Despite the fact that the art recognized the difficulties associated with the genetic modification of **human ES cells,** the only guidance specific to **human** ES cells is found in Example 6, where the specification directs the skilled artisan to use **adenovirus** to transduce **human** ES cells. As pointed out in previous Office Actions, no results are provided for the adenovirus transduction experiments. The instant specification only teaches how to produce dopaminergic neurons from mouse ES cells, and mouse neurons are not suitable for transplantation into human patients. Mouse ES cells are not human ES cells. They exhibit widely varying characteristics compared to human ES cells and therefore have not been predictive of the behavior of human ES cells.

The behavior of mouse ES cells is not predictive of human ES cells. As discussed in the previous Office Action, mouse ES cells behave quite differently from human ES cells. Human ES cells have different characteristics and require the development of different protocols for their genetic modification, culture, and *in vitro* differentiation. Odorico et al. (2001) provides a discussion of multilineage differentiation from human embryonic stem cells and points out that many barriers remain in the way of successful clinical trials that employ the transplantation of human ES cells or ES cell-derived cells. The reference provides a detailed discussion of the differences between human ES cells and mouse ES cells. The reference points out that human and nonhuman primate ES cells share a similar

morphology that is distinct from mouse ES cells (page 194, column 2, paragraph 2). Furthermore, human ES cells grow more slowly than mouse ES cells (page 194, column 2, paragraph 2). Human ES cells differ from murine ES cells with regard to cell-surface antigen phenotype (page 195, column 1, paragraph 1). Human ES cells also differ from mouse ES cells in their *in vitro* culture requirements for undifferentiated growth (page 195, column 1, paragraph 2). Mouse ES cells require leukemia inhibitory factor (LIF) for undifferentiated proliferation, whereas LIF alone is not sufficient to prevent differentiation of human ES cells *in vitro* (page 195, column 1, paragraph 2). It is important to note that, directed differentiation of ES cells results in mixed populations of cells. Odorico et al. points out that the heterogeneous nature of development in culture has hampered the use of ES cell derivatives in transplantation studies (page 198, column 2). The reference further emphasizes that achieving a therapeutic result will mandate integration of the transplanted cells into the host tissue in a functionally useful form (page 199, column 2). The reference acknowledges the complex structural integration required for transplantation into the neuronal circuitry (page 200, column 1, paragraph 1).

At page 8, paragraph 2 of the response, Applicants assert that the specification is not limited in its teaching by the presence of the specific embodiment of Example 6. Applicants allege "[n]owhere in the specification is it stated that one must use an adenovirus vector to achieve transfection of human ES cells." Nevertheless, the **only** specific guidance with regard to the transfection of **human** ES cells is to use an adenoviral vector, as set forth in Example 6 of the specification. Furthermore, it is noted that general guidance cannot substitute, where specific guidance is required. In cases involving unpredictable factors, it is the role of the specification to provide the **specific** guidance necessary for the skilled artisan to carry out the entire protocol with a predictable degree of success. The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement

varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

At page 8, paragraph 3 of the response, Applicants assert that "the examiner concedes that Eiges et al. ... demonstrates that Lipofectamine was a successful, albeit inefficient, method for transfection of human ES cells" citing page 5 of the Office Action. The Examiner does not agree with this characterization of the previous response to Applicants' arguments regarding Lipofectamine transfection. The Office Action states that "Eiges had already demonstrated that Lipofectamine was a very inefficient method for transfecting human ES cells, thereby teaching away from the use of Lipofectamine-mediated transfection" (page 5, last sentence of the Office Action mailed 11/2/04). It can hardly be said that such a statement concedes that Lipofectamine was "successful." It does not. Figure 1 of Eiges et al. shows that, upon Lipofectamine-mediated transfection of human ES cell cultures, expression of luciferase was at the same level as control cultures transfected with the luciferase gene (control cultures are MEF-only controls as stated in the legend to Figure 1). The only conclusion that one of skill in the art would draw from such experiments is that **no transfected ES cells were detected** upon Lipofectamine-mediated transfection of human ES cell cultures.

At page 8, paragraph 4 and page 9, paragraph 1 of the response, Applicants assert that inefficient transfection is sufficient to practice the claimed methods because all that is required "is that some transfection of ES cells is achieved, however inefficient, followed by isolation and expansion of the transfected cells." Applicants point to the specification at page 3, line 21 to page 4, line 12 for providing guidance for isolating homogeneous cell populations. Again, the guidance provided at pages 3-4 of the specification is in the form of general guidance, which can be applied to mouse ES cells or any other species of ES cell, but is not specific to human ES cells. The discussion at pages 3-4 is directed to a strategy for producing homogeneous cell populations by inserting a selectable gene cassette into the dopamine transporter (DAT) gene or tyrosine hydroxylase (TH) gene. Applicants state that "[b]ecause

specific lineage-restricted neural precursors can be isolated and expanded as a pure population, the efficiency of transfection is irrelevant to the enablement of the claimed methods." Nothing could be further from the truth. How can the efficiency of transfection be irrelevant to enablement of the claimed methods when the **strategy** for producing said "pure population" **relies on** transfecting the cells with a selectable gene cassette? Poor transfection methods result not only in a low number of genetically modified cells, but also **transient expression** of the gene that is introduced, if any at all. Since the strategy for producing said "pure population" of cells relies on expression of an antibiotic resistance gene, sufficient expression of the gene is needed to produce an expanded population of the desired cell type. **Transient expression** occurs when non-integrating vectors are lost during subsequent cell division. Thus, it is not convincing to suggest that all that is required is to obtain one cell that survives the transfection and selection protocol and then to expand that cell, under selective conditions, to produce sufficient numbers of cells of the desired phenotype for transplantation. To obtain "expansion of the transfected cells" as Applicants argue, the progeny cells must **continue** to express the transgene. No support is offered for the suggestion that the transfected cells could be expanded to create a pure population of the desired cell type. You cannot continue to expand the desired cell type under selection conditions when the desired cell type loses expression of the selection marker.

At page 9, paragraph 2 of the response, Applicants continue to assert that the art cited by the Examiner demonstrates that the specification, combined with techniques and reagents available at the time of filing, enables the genetic modification of human ES cells. However, with regard to **human** ES cells suitable for use in the claimed invention, the specification teaches that the cells should be transduced using adenovirus. ExGen 500 is not contemplated as a transfection method that would be useful in the claimed method of the invention. Even as late as 2005, Moore et al. (2005) acknowledges that "a major hurdle has been the resistance of [human embryonic stem cells] to established infection and chemical transfection methodologies to introduce ectopic genes" (abstract). Xiong et al. (2005) echoes this

characterization, stating "[w]hile differentiation may be controlled by the genetic manipulation, effective and efficient gene transfer into hES cells has been an elusive goal" (abstract). Thus, even the post-filing art readily acknowledges the continuing problem of genetic modification of human ES cells.

At page 9, paragraph 4 of the response, Applicants assert that therapeutic transplantation is enabled because the therapeutic effect is conferred by the cell, not by the gene. Applicants assert that the expression of a cell fate-inducing gene by the ES cell is merely to promote differentiation along a dopaminergic cell fate pathway and is performed primarily in culture prior to transplantation. Applicants note that Figure 5B demonstrates that Nurr-1 expression *in vitro* urges a higher proportion of cultured ES cells to adopt a dopaminergic phenotype, compared to cultured naïve ES cells. Since Applicants' arguments are not commensurate in scope with the scope of the claims, it appears that Applicants are arguing that there is a scope of enablement for differentiating the ES cells *in vitro* prior to transplantation to produce dopaminergic neurons which are then transplanted to the brain to produce a therapeutic effect. However, the rejection of record points out that substantial obstacles exist in the field of therapeutic transplantation to the central nervous system (CNS). As noted in the prior Office Actions, Jackowski (1995) details the limitations and unpredictability associated with the transplantation of neural tissue into the CNS. Thus, even if the claims were limited to developing the dopaminergic phenotype *in vitro* prior to transplantation (which they are not) and even if the rest of the enablement rejection were overcome, the barriers to therapeutic transplantation of fully differentiated neurons into the brain remain, for reasons of record.

At page 10, paragraph 1 of the response, Applicants assert that the dopaminergic-inducing effect of expressing a cell fate-inducing gene *in vitro* is complemented by transplantation of the ES cell into the brain. Applicants further note that naïve ES cells differentiate along a dopaminergic cell fate pathway upon transplantation into the brain, as demonstrated by Deacon et al. and Example 13, page 35 of the specification. Thus, Applicants note, the transplanted ES cells differentiate *in vivo* regardless of whether

they express a cell fate-inducing gene. Applicants assert that it is the cell, not the gene, which confers the therapeutic effect and, because the phenotypic change in the ES cell can be monitored *in vitro* prior to transplantation, no guidance on *in vivo* gene expression is required. It is unclear what aspect of the rejection this argument is intended to address. Furthermore, it is unclear which claims Applicants are arguing because, contrary to Applicants' assertion, the vast majority of the claims **require** genetic modification (see Claims 1, 4, 17-24, 25-29, 31, and 32). Only Claims 16 and 30 encompass the use of cells that have not been genetically modified, i.e. naïve ES cells. Where Claim 16 covers the use of naïve ES cells, one could not monitor "the phenotypic change in the ES cell ... *in vitro* prior to transplantation" because the claimed method ***requires*** the implantation of undifferentiated ES cells "such that the cells form, in the patient, a population of cells in which at least 90% the cells are dopaminergic neurons." Where Claim 30 covers the use of dopaminergic neurons the have not been genetically modified, the claim explicitly recites that those cells were "cultured from isolated embryonic stem cells" but the specification does not teach how to produce "a population of cells in which at least 90% of said population of cells are dopaminergic neurons" *in vitro* in the absence of genetic modification with a cell fate-inducing gene. Thus, Applicants' statement that "no guidance on *in vivo* gene expression is required" is not commensurate in scope with the scope of the claims. At least claims 17 and 18 ***require in vivo*** expression of the cell fate-inducing gene and the remaining claims ***cover*** the *in vivo* expression of the cell fate-inducing gene to obtain the desired cell type.

At page 10, paragraphs 3 and 4 of the response, Applicants assert that the ES cell compositions described in the specification become functioning neurons upon transplantation. Applicants point to Examples 12-14 for demonstrating that naïve ES cells spontaneously adopt a neuronal phenotype when transplanted into the brain and that dopaminergic differentiation of naïve ES cells was observed in two different rodent models of Parkinson's disease – the MPTP mouse model (Examples 12 and 13) and the 6-OHDA lesioned rat model (Examples 14 and 15). However, for the reasons discussed above, the art

teaches that the directed differentiation of **human** ES cells leads to a heterogeneous mixture of cells (Odorico et al., page 198, column 2) and the instant specification does not teach how to use a mixed population of cells for therapeutic transplantation. Mouse ES cells are not human ES cells. They exhibit widely varying characteristics compared to human ES cells and therefore have not been predictive of the behavior of human ES cells. Thus, the rejection is not based on the lack of correlation between the animal model and the human condition, but rather is based on the lack of correlation between mouse ES cells and human ES cells. The instant specification teaches that **human** ES cells should be used in humans and one of skill in the art would not attempt to use **mouse** ES cells in humans. Thus, specific teachings with regard to the manipulation and characterization of human ES cells are needed before therapeutic transplantation can become a reality.

At page 11, paragraph 2 of the response, Applicants assert that the specification demonstrates that transplantation of ES cells improves motor function. Applicants point to Examples 14 and 15 and Figure 7 for showing reduced amphetamine-induced turning in unilateral 6-OHDA-lesioned rats after transplantation of mouse ES cells (i.e., naïve ES cells). While naïve mouse ES cells were effective in a rat model of Parkinson's disease (PD), it is again noted that mouse ES cells are not human ES cells. As discussed in the prior Office Action, one of the critical elements is developing appropriate cell compositions for therapeutic transplantation (page 8, paragraph 3 of the Office Action of 11/2/04). The experiments described in the specification fail to permit the skilled artisan to obtain a cell composition derived from **human** ES cells that is suitable for transplantation into human patients. The specification does not provide sufficient guidance regarding which promoters are active in human ES cells or a teaching of which promoter should be used to drive expression of Nurr1 and/or PTX-3. As a prerequisite to cell transplantation, the skilled artisan must be able to produce the cell compositions that will be transplanted. Thus, the specification fails to teach the skilled artisan how to obtain **cell compositions** that are suitable for transplantation into humans. The art teaches that the directed differentiation of ES cells

leads to a heterogeneous mixture of cells and the instant specification does not teach how to use a mixed population of cells for therapeutic transplantation. Mouse ES cells exhibit widely varying characteristics compared to human ES cells and therefore have not been predictive of the behavior of human ES cells. The instant specification does not provide sufficient guidance for obtaining the necessary cell compositions, by routine experimentation, appropriate for production of a therapeutic effect in a PD patient, for reasons of record. The instant specification only teaches how to produce dopaminergic neurons from mouse ES cells, and mouse neurons are not suitable for transplantation into human patients.

Thus, the rejection under 35 U.S.C. 112, first paragraph, is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 29 is indefinite in its recitation of "wherein said stem cells are embryonic stem cells" because Claim 25 already recites that the stem cells are "recombinant embryonic stem cells."

Claim 29 is further indefinite in its recitation of "wherein said stem cells ... are cultured from embryonic stem cells transfected with a nucleic acid encoding Nurr-1 and PTX-3" because it is unclear how the "recombinant embryonic stem cells" (of Claim 25) can be "cultured from embryonic stem cells transfected with a nucleic acid encoding Nurr-1 and PTX-3" since the "recombinant embryonic stem cells" are undifferentiated cells, but Nurr-1 and PTX-3 are cell fate-inducing genes. Therefore, how can undifferentiated embryonic stem cells be "cultured from embryonic stem cells transfected with a nucleic acid encoding Nurr-1 and PTX-3"?

Conclusion

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk
ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER